UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/893,244	06/27/2001	Barry S. Fogel	0264724-0031	4907

20995 7590 10/25/2005

KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
WILLIAMS, LEONARD M	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 10/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/893,244	FOGEL, BARRY S.	
	Examiner	Art Unit	
	Leonard M. Williams	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *81-83 and 85-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *81-83 and 85-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 9/28/2001
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Response to Amendment

The examiner notes the receipt of the amendments and remarks received in the office on 7/25/2205 canceling claims 1-62 and 84, amending claims 81, 82, 85 and 88, and adding new claims 89-90. Claims 81-83 and 85-89 are currently pending.

The amendment of claim 81 to recite " a composition comprising...a first active..." is sufficient to overcome the 112-1 enablement rejection of claims 81-84 presented in the office action of 2/24/2005.

The amendment of claim 82 to recite "wherein said first and second moieties are covalently linked" is sufficient to overcome the 112-2 rejection of claim 82 presented in the office action of 2/24/2005.

The amendments made and the addition of claims 89 and 90 necessitate the withdrawal of the 102(b) rejection over claims 81-84 and the 103(a) rejections over claims 85-88. New rejections over claims 81-83 and 85-90 are detailed below after the response to arguments.

Response to Arguments

Applicant's arguments with respect to claims 81-88 have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendment of the claims.

The examiner notes that in response to the 103(a) rejection of claims 85-88 applicants asserted on page 7 first paragraph that there existed secondary conditions not considered by the examiner, specifically unexpected results. The examiner respectfully disagrees. The applicant's specifically state that the combination of acamprosate and magnesium was unexpectedly synergistic and beneficial. The applicant's set forth studies 2-5 as evidence of the unexpected synergistic effects.

Churchill's Illustrated Medical Dictionary (1989) defines synergism as "the state of acting together, especially so that the combined action of all participating elements is greater than that of each element if acting separately: said groups of muscles or chemicals". The examiner respectfully points out that the studies presented are not structured in such a way that synergism can be determined. To elucidate this point the examiner will present an analysis of Case Report 2.

Case Report 2 deals with a 79-year old woman with long-standing tardive dyskinesia (TD) after years of neuroleptic drug therapy. The patient was treated with memantine and showed improvement with a continuation of a mild-to-moderate level of TD. The patient also took antiepileptic drugs, antiplatelet drugs, and medications for hypertension, glaucoma, and gastrointestinal disorders. The applicant's assert these medications did not affect the patient's TD. The patient was then treated with acamprosate (666mg 3 X daily) in addition to the memantine and additional drugs with no stoppage of the memantine before addition of acamprosate. The applicant's assert that the patients TD symptoms and memory improved after addition of the acamprosate. After one year the memantine was discontinued and the applicant's state on page 38,

"...the memantine was discontinued, with little change in the patient's symptoms." Magnesium oxide was then added to the acamprosate and the patient's symptoms improved. The applicant's state that the patient's movements worsened when the magnesium oxide was stopped and improved when started back.

The examiner wishes to note first that each of these studies detail only one patients experience with no clinical statistical evaluation.

The applicant's treated the patient first with memantine and there was an improvement in the patients TD symptoms. The patient was additionally treated with acamprosate in addition to memantine and further improvement of symptoms was noted. The memantine was then stopped and by applicant's own admission (pg 38) there was little change in the patient's symptoms. This would argue that all the improvement seen in the concurrent use of acamprosate and memantine was solely from the acamprosate i.e., no synergism. The subsequent addition of magnesium oxide to the acamprosate and further improvement of the symptoms could additionally be due solely to the effect of the magnesium oxide as the withdrawl of the magnesium oxide resulted in the worsening of symptoms, but no such evidence was reported involving the withdrawl of the acamprosate while maintaining the magnesium oxide.

In order to show synergism the applicant's would need to show a baseline improvement in a single patient with acamprosate by itself. Then cease the acamprosate and begin memantine to achieve a baseline improvement with only memantine. Then cease memantine and begin a magnesium regimen to show a base line improvement with only magnesium. Once this was accomplished then

combinations of acamprosate, memantine and/or magnesium would be evaluated and if a synergistic effect was noted then there would be evidence such as being able to use lower dosages of the individual drugs in combination to achieve the same (or better) baseline improvement over the individual drugs.

The examiner respectfully points out that all the studies fail to show evidence of synergistic effects of the drugs due to similar failings in their design.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 82 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for acamprosate, memantine and magnesium salts (and chelates), does not reasonably provide enablement for covalently linked derivatives of these compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547

the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the ad; (4) the predictability or unpredictability of the ad; (5) the breadth of the claims', (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention:

The rejected claim is drawn to "The composition...wherein said first and second moieties are covalently linked".

(2) Breadth of the Claims:

The breadth of the claim is exceptionally broad encompassing any and all means of covalently linking the first and second moiety.

(3) Guidance of the Specification:

The guidance of the specification as to "The composition...wherein said first and second moieties are covalently linked" is limited to page 20 lines 21-23 of the specification stating:

"The combinations may be either mixtures, covalently-bound moieties with combined action, or pro-drugs metabolized in the blood, liver, or brain to release each member of the combination."

No examples are mentioned. No methods detailed.

(4) Working Examples:

The applicant provides no working examples in case reports 1-6 as all the compounds used are individual compounds and not covalently linked in any fashion.

(5) State/predictability of the Art:

The state of the art regarding the covalent linking of two agents (especially pharmaceutically active agents) is high.

(6) The Quantity of Experimentation Necessary:

The instant claims read on any type of covalent linkages of molecules. There are no examples given representing a covalent linkage between any of the active molecules, much less evidence to show that a covalently linked compound comprising two of the active agents would preserve the individual agents activities. Applicant fails to provide information sufficient to practice the claimed invention, absent undue experimentation (i.e. experimenting with all compositions having at least two agents). Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Accordingly the claim is rejected.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 81-83 and 85-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lidsky (US Patent No. 5602150), in view of Vetulani (Review Drug Addiction. Part III. Pharmacotherapy of Addiction, Polish Journal of Pharmacology, 2001, Vol. 53, pp. 415-434), in view of Bormann et al. (US Patent No. 5061703) and further in view of Decollogne et al. (NMDA Receptor Complex Blockade by Oral Administration of Magnesium: Comparison with MK-801, 1997, Pharmacology Biochemistry and Behavior, Vol. 58, No. 1, pp. 261-268).

Lidsky et al. teach in, the abstract and col. 10 lines 35-65, a method of treatment and a composition to prevent the development of the adverse manifestation of tardive dyskinesia in patients undergoing treatment with a neuroleptic or antipsychotic agent comprising administering the neuroleptic or antipsychotic agent with taurine, a taurine precursor, taurine derivative, or compounds similar in action to taurine including acamprosate (as evidenced by applicant's own admission, see current specification page 23, line 25).

Lidsky does not teach that acamprosate is to be administered with a second active moiety comprising an NMDA-type glutamate antagonist, nor exactly by what mechanism acamprosate and the other taurine derivatives work.

Vetulani teaches, on page 424, that acamprosate acts as both a GABAergic neurotransmitter enhancer and as an antagonist of glutamatergic neurotransmission via

the NMDA receptor. Thus acamprosate is both a GABA agonist and a NMDA antagonist.

Bormann et al. teach, in col. 2 line 60 to col. 3 line 25, heterocyclic, aromatic compounds exhibiting NMDA receptor channel-antagonistic and anticonvulsive properties including 1-amino-3,5-dimethyl adamantane (memanatine).

Decollogne et al. teach, in the abstract and on page 265, that oral treatment with a single dose of magnesium organic salts (such as magnesium aspartate, magnesium lactate) leads to an increase in serum Mg2+ concentration and that magnesium is a noncompetitive ion-channel blocker of the NMDA receptor complex.

It would have been obvious to one of ordinary skill in the art at the time of the invention was made that acamprosate (a GABA agonist and NMDA-receptor antagonist), memantine (an NMDA-receptor antagonist), and magnesium (an NMDA-receptor antagonist) targeted the same receptor pathways. Additionally Lidsky demonstrated that acamprosate was effective in the prevention of tardive dyskinesia associated with neuroleptic and antipsychotic drugs. One of ordinary skill would know that compounds targeting the same receptor have similar activities and could be used in the treatment of similar conditions.

The examiner respectfully points out the following from MPEP 2144.06:
"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from

their having been individually taught in the prior art." *In re* Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leonard M. Williams whose telephone number is 571-272-0685. The examiner can normally be reached on MF 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

LMW

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER